REMARKS/ARGUMENTS

Reconsideration of this application is requested.

The claims are 1 to 7 and 9 to 20.

The above amendment is responsive to points set forth in the Official Action.

Support for Amendments

In claim 9, the definition of X has been amended such that the dimeric and oligomeric species are excluded from the claim. In addition, the definition of substituent Y has been amended to exclude the possibility that it is alkyl, both substituted and unsubstituted, as well as unsubstituted alkenyl or unsubstituted aralkyl. Support for this amendment is provided at page 2 line 14 and page 3 lines 7 to 9. As a consequence of this limitation to claim 9 the proviso is redundant. It has therefore been cancelled.

New claims 11 to 18 have been added which are dependent on claim 9. Claims 11, 12 and 15 find support in claims 2, 3 and 4, respectively. Claim 13 finds support on page 3 line 22. Claim 14 finds support on page 3 line 25. Claim 16 finds support at page 4, lines 3 and 18. Claim 17 finds support at page 5 line 10 together with page 6 line 17. Claim 18 finds support at page 5, line 16 together with page 6 line 17.

New claims 19 and 20 have been added, each directed to a method of medical treatment. Claim 19 specifies the treatment of a patient in need of an inhibitor of human thioredoxin reductase. This claim is supported at page 7 lines 21 to 23, page 7 lines 13 to 17 and page 15 line 29 to page 17 line 7. Support for claim 20 is provided on page 7 lines 21 to 24, 27 and 28.

Rejection under 35 USC 103

Claims 1 to 7, 9 and 10 stand rejected under this heading as unpatentable over McFadyen

(1986) in view of McCoubrey, McFadyen (1987), Peyratout and Mureinik. Applicant respectfully traverses this rejection.

The Examiner states that McFadyen (1986) teaches platinum (II) terpyridine complexes of "the same type" recited in the claims. Whilst it is acknowledged that the compound denoted M-4 in Figure 1 on page 757 of McFadyen is within formula (I) of present claim 1, it is outside the scope of claim 9 as amended owing to the cancellation of the possibility that Y is alkyl. Likewise, the compound denoted D-*n*, whilst within the formula defined in claim 1, is outside the scope of claim 9 as now amended owing to the exclusion of dimeric species from the claim.

McFadyen does not teach or suggest a method of medical treatment using the compounds which it discloses. Rather, the authors focus on the synthesis and characterization of the compounds and an examination of their ability to intercalate with DNA. The document therefore provides no incentive for a person of skill in the seek to employ the compounds in a method of treatment of a human or animal body.

There is also no reason why a person of skill in the art would modify the compounds disclosed in McFadyen in such a way that they fall within the scope of claim 9 as now amended. The teaching of McFadyen fails to make any such structural modification obvious, whether taken alone or in combination with the other cited documents. The specific compounds disclosed in the other references all correspond to formula (I) in which Y is unsubstituted or substituted alkyl, chloro or hydroxy. From these it would certainly not be obvious to arrive at the definitions of Y according to claim 9 as now amended.

The Examiner has alleged that McCoubrey teaches "analogous complexes" to those of the present invention. Whilst it is acknowledged that the compounds of formula (I) on page 73, identified by the Examiner, are indeed "analogous" to compounds of present formula (I), their disclosure does not make it obvious to arrive at compounds within present claim 9. Likewise, since McCoubrey describes an investigation into the intercalation properties of particular platinum (II) complexes, it fails to teach or suggest a method of actively

treating the human or animal body. There would therefore be no incentive for a person of skill in the art to contemplate the use of the disclosed compounds in a method of therapy. Accordingly, claim 1 is non-obvious over this reference.

McFadyen (1987) teaches the same compounds as the McFadyen (1986) reference discussed above. Accordingly, the arguments set forth above in respect of the first McFadyen reference apply here too. The rejection based on McFadyen (1987) is accordingly believed to be unfounded and should be withdrawn.

Mureinik is an academic article concerned solely with the synthesis of terpyridyl complexes of platinum (II) and an investigation of their physicochemical properties. There is no teaching or suggestion that the compounds should be used in a method of therapy, so the reference fails to render claim 1 obvious. Likewise, the reference provides no motivation for a skilled person to modify the disclosed compounds in such a way as to arrive at a compound falling within claim 9 as now amended. There would be no reason to make such a modification in the first place, still less any reason to make the modification in the expectation of achieving compounds which are inhibitors of thioredoxin reductase.

The Examiner has alleged that the use of different but otherwise analogous substituents in place of those taught in the reference would not have been unexpected, particularly in view of Peyratout. Peyratout discloses two platinum (II) terpyridine complexes, namely Pt (trpy) OH^+ and Pt (trpy) Het^+ in which Het is 2-hydroxyethanethiol. The latter compound corresponds to present formula (I) in which each X is hydrogen and Y is alkyl (i.e. ethyl). As with the other cited references, this disclosure is outside the scope of claim 9 as now amended owing to the exclusion from claim 9 of compounds in which Y is alkyl. Nothing taught by Peryratout suggests to a skilled person that the disclosed compound should be structurally modified. There is certainly nothing to suggest that the compound should be modified in such a way as to arrive at a compound within present claim 9 in the expectation that such a compound would be an inhibitor of thioredoxin reductase and therefore useful as an anti-tumor, antiprotozoal or anti-rheumatoid arthritis agent.

With the exception of Mureinik, the cited references all teach that the platinum (II) complexes to which they relate either are, or may be, intercalating agents. Whilst it is therefore apparent that some thiolato-terpyridine platinum complexes are known to be intercalators of DNA it is quite wrong to conclude that, in consequence, these complexes will possess anti-tumor activity. At the present filing date there was no demonstration in the literature that intercalation into DNA was the cause of anti-tumour activity. Indeed, results have shown that intercalation activity is no reliable guide as to likely anti-tumor activity. Thus, to take a specific example, hydroxyethane thiolato-terpyridine platinum (II) complexes bind less effectively to DNA by intercalation than does the 4-picoline terpyridine platinum (II) complex; the equilibrium binding constant of the former is 0.83 x 10^5 M^{-1} while that of the latter is 2x 10^7 M^{-1}. The equilibrium binding constant of the picoline compound is consequently over 200 times greater than that of the hydroxyethane thiolato complex. This can be attributed to the fact that the former is singly positively charged while the latter is doubly positively charged. Nonetheless, the anti tumor activity of the thiolato complex is comparable to, or greater than, that of the 4-picoline terpyridine platinum (II) complex.

The applicant has in fact demonstrated that human thioredoxin reductase is irreversibly inhibited by the claimed thiolate complexes. In tumor cells treated with these complexes the thioredoxin reductase activity is diminished. Furthermore, this lowering of activity correlates with anti-proliferative activity. Thus, Applicant has found the target for this class of compound. In this connection the Examiner is referred to the results of anti-tumor activity given in the specification, along with a discussion of the results, on page 42 to 45 and in tables 5 to 9. As indicated in the passage bridging pages 42 and 43, it is believed that the reason thioredoxin reductase can displace the thiolate from the terpyridine platinum (II) complex is that the active site consists of the rare selenocysteine residue which has a higher affinity for platinum (II) than does a thiolate and which therefore becomes irreversibly inhibited.

To conclude, therefore, Applicant has found the key requirement for anti tumor activity in compounds of the present type. Until that recognition had been reached there would have

been no objective reason, based on the cited prior art references, for modifying the prior art platinum (II) complexes in such a way as to arrive at those within present claim 9 in the expectation that they would have useful therapeutic applications.

The above comments show that, despite the Examiner's assertions, there was no rationale or motivation in the art at the present filing date for a person of skill in the art to arrive at the claimed invention. Accordingly, withdrawal of the outstanding rejection is requested.

Respectfully submitted,

WENDEROTH, LIND & PONACK LLP

By: _____

Matthew Jacob
Registration No. 25,154
Attorney for Applicant

MJ/ke
2033K St, N. W. Suite 800
Washington DC 20026-1021 USA
Telephone: 202 721 8200
Facsimile: 202 721 8250
August 20, 2004